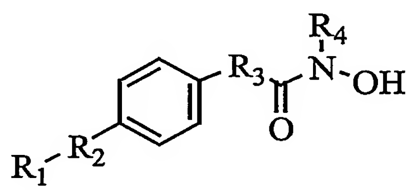
HYDROXAMIC ACID DERIVATIVES AND THE METHOD FOR PREPARAING THEREOF

FIELD OF THE INVENTION

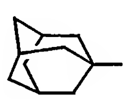
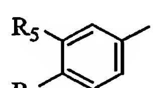
The present invention relates to hydroxamic acid derivatives represented by the following formula (I), having anti-aging efficacy and to a method for the preparation thereof :

[Formula 1]



(I)

wherein,

R_1 is  or , herein, R_5 and R_6 each independently represents a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms or a cyclic alkyl group having from 3 to 6 carbon atoms;

R_2 is CONH, NHCO, $CONR_7$ or NR_7CO, herein, R_7 represents an alkyl group having from 1 to 10 carbon atoms;

R_3 is $-(CH)_n-$, herein, n = 0 or 1; and

R_4 is a hydrogen atom or an alkyl group having from 1 to 10 carbon atoms.

BACKGROUND OF THE INVENTION

The skin of all living things grows aged as it grows older. In order to delay this skin aging, many efforts have been made extensively. As a result, the questions on the essence and cause of the aging have always been raised. Skin aging is classified into two kinds depending on its cause. The first is intrinsic aging that the structure of and the physiological function of the skin decline successively as aging goes on. And, the second is extrinsic aging that is caused by accumulated stress such as UV radiation. Particularly, UV radiation is well-known cause of aging. In case of the skin exposed to UV radiation for a long time, stratum corneum of the skin becomes thicker and collagen and elastin, which are main components of the skin, get denatured so that skin loses its elasticity. Thus, skin aging is accompanied by several functional and structural changes.

As structural changes caused by skin aging, epidermis, dermis and hypoderm of the skin become thinner. And, dermal ECM (extracelluar matrix), which is in charge of skin elasticity and elongation, is experienced with its component's change. ECM is composed of two components, i.e. elastic fiber which amounts to 2~4% of total ECM and collagen which amounts to 70~80%. As skin aging goes on, the skin loses elasticity due to the reduction of collagen and elastin. These reductions are caused by several factors in biosynthesis. For example, matrix metallo proteases, such as collagenase and elastase, are expressed to decompose collagen and elastin, and the collagen content within the skin is reduced. The reduction of collagen and elastin within the dermis leads the epidermis to be rough and to lose elasticity. That is, the skin becomes aged.

In order to suppress the reductions of collagen and elastin, which are a cause of the skin elasticity reduction, some materials have been developed and used. Specially, retinoid such as retinol and retinoic acid has been known to be very effective in lessening skin wrinkles and improving skin elasticity (*Dermatology therapy*, 1998, 16, 357~364). In spite of its anti-wrinkle efficacy and

elasticity-improving efficacy, retinoid has some drawbacks that only a small quantity of application causes irritation to the skin and is easily oxidized in an air due to its instability, thus there are lots of limitation in using it. In order to stabilize retinoid, many studies have been conducted. However, the irritation of retinoid onto the skin, that is troubles in safety onto the skin, remains unsolved.

Retinoid includes retinol, retinoic acid or its derivatives. It exhibits various biological activities. With regard to the skin, the efficacy on abnormal keratinization or on pimple was reported. And, with regard to the skin wrinkles, it has been known that it can promote collagen biosynthesis and inhibit the activity of collagenase, i.e. an enzyme for decomposing collagen (*The Journal of Investigative Dermatology*, 1991, 96, 975~978). In addition, retinoid can inhibit the expression of elastase, with regard to the elasticity-reduction.

Up to now, retinoid has been developed as follows:

In the first stage, simple derivatives of retinol or retinoic acid were developed. As a derivative, retinyl palmitate may be exemplified. In the next, retinoid derivative including benzoic acid was developed. This derivative is named as arotinoid (*J. Med. Chem*, 1988, 31, 2182~2192). Recently, compounds including heteroatom introduced into the benzene ring of arotinoid, called as heteroarotinoid, have been developed (*J. Med. Chem.*, 1999, 42, 4434~4445).

Retinoid was reported to exhibit biological efficacy on the skin by interacting with the intercellullar receptor called as retinoic acid receptor (*British Journal of dermatology*, 1999, 140, 12~17). The structural feature of retinoid is based on tetramethyl cyclohexane, unsaturated carbon bond and carboxylic acid. Specially, carboxylic acid moiety is essential in the action of retionids and can be easily converted into an anion when interacting with the receptor (*Chem. Pharm. Bull*, 2001, 49, 501~503).

Arotinoid includes benzoic acid substituted for carboxylic acid moiety of retinoic acid. Benzoic acid moiety can be easily ionized to act as an anion.

Recent studies have synthesized derivatives including various substituents for carboxylic acid moiety. These substituent-conversions are in order to maintain original efficacy of retinoid and to lessen toxicity or irritation and instability thereof. For the purpose, many studies have been conducted.

SUMMARY OF THE INVENTION

Under these circumstances, the present inventors have conducted many studies in order to lessen skin irritation of retinoid and to provide a solution for instability in external formulations for skin care. As a result, we synthesized a novel type of retinoid, i.e. hydroxamic acid derivatives. Furthermore, we found that these hydroxamic acid derivatives had good safety to the skin and improved stability in the formulations, without skin irritation and discoloration and odorizing, caused by the conventional retinal or retinoic acid. Based on these findings, the present invention has been completed.

Therefore, an object of the invention is to provide novel hydroxamic acid derivatives, which function as a retinoid to promote collagen biosynthesis and to inhibit the expression of collagenase, i.e. an enzyme for decomposing collagen and the expression of elastase, i.e. an enzyme for decomposing elastin, and to provide a method for preparing the same.

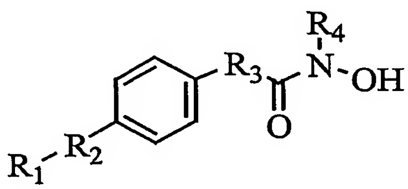
Hydroxamic acid has been widely known as a metal chelator. Judging from the structural feature of hydroxamic acid, hydroxy group of hydroxylamine adjacent to carbonyl group forms chelation with metal cation.

In additional feature, hydroxy group of hydroxylamine can be easily converted into an anion, to be used in similar to carboxylic acid. The present inventors utilized these structural features of hydroxamic acid to synthesize a novel retinoid and found that it functioned as an agonist to retinoic acid receptor. Such a compound having the stucture of hydroxamic acid and functioning as a

retinoid has not been reported yet.

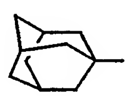
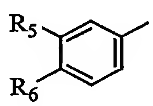
The present invention relates to hydroxamic acid derivatives represented by the following formula (I) :

[Formula 1]



(I)

wherein,

R_1 is  or , herein, R_5 and R_6 each independently represents a hydrogen atom, a C_1-C_{10} alkyl group or a C_3-C_6 cyclic alkyl group;

R_2 is CONH, NHCO, $CONR_7$ or NR_7CO, herein, R_7 represents a C_1-C_{10} alkyl group;

R_3 is $-(CH)_n-$, herein, n = 0 or 1; and

R_4 is a hydrogen atom or a C_1-C_{10} alkyl group.

The novel type of retinoid in the present invention, hydroxamic acid derivatives may be prepared by either of two methods exemplified below.

In detail, the method for preparing said hydroxamic acid derivatives represented by said formula (I) may comprise the steps of :

(1) Reacting benzoic acid or adamantanecarboxylic acid with methyl 4-aminobenzoate or 4-aminophenylacetic acid methylester, to form an amide bond; or reacting aniline or adamantamine wih monomethylterephthalate, to form an amide bond;

(2) Substituting an alkyl group for amide bond of benzamide formed in said step;

(3) Hydrolyzing the ester bond of benzamide or alkyl-substituted benzamide formed in said steps; and

(4) Converting the acid formed by said hydrolysis to a hydroxamic acid.

Specially, in the last step of producing a hydroxamic acid derivative, one-step processing without protective/deprotective reactions is used to increase efficiency.

DETAILED DESCRIPTION OF THE INVENTION

The following is a detailed description of the present invention.

The present hydroxamic acid derivative, as a novel retinoid, may be prepared by either of two methods exemplified below.

The first method 1 may comprise the steps of:

(a) Reacting benzoic acid or adamantanecarboxylic acid with methyl 4-aminobenzoate or 4-aminophenylacetic acid methylester, to produce a benzamide compound;

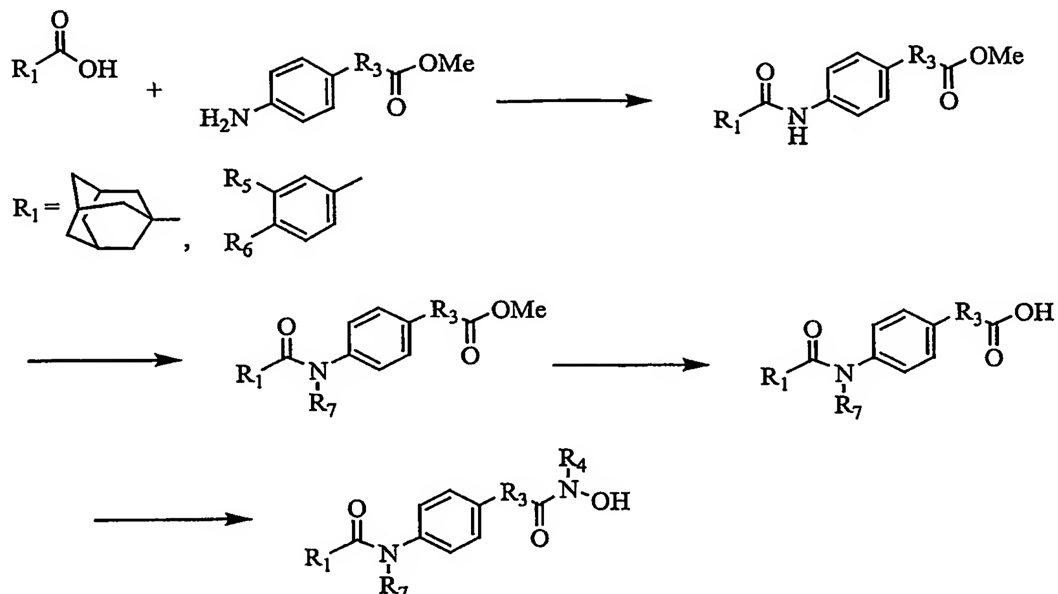
(b) Substituting an alkyl group for amide bond of benzamide formed in said step;

(c) Hydrolyzing methylester of benzamide or alkyl-substituted benzamide compounds formed in said steps, to produce an acid; and

(d) Reacting said acid with hydroxylamine hydrochloride or N-methyl hydroxylamine hydrochloride, to produce a hydroxamic acid derivative.

Said method of the present invention will be described in more detail by the following reaction scheme. Firstly, said method 1 may be exemplified by the following reaction scheme 1:

[Reaction Scheme 1]



(I)

wherein, R_5 and R_6 each independently represents a hydrogen atom, a C_1-C_{10} alkyl group or a C_3-C_6 cyclic alkyl group; R_2 is CONH, NHCO, $CONR_7$ or NR_7CO, herein, R_7 represents a C_1-C_{10} alkyl group; R_3 is $-(CH)_n-$, herein, n = 0 or 1; and R_4 is a hydrogen atom or a C_1-C_{10} alkyl group.

In the first place, benzoic acid or adamantanecarboxylic acid may be converted to an anhydride by employing ethyl chloroformate in an equivalent ratio of 1.2. A solvent employed herein may be pyridine, N-methylmorpholine and the like. Then, the anhydride may be reacted with methyl 4-aminobenzoate or 4-aminophenylacetic acid methylester, to produce a benzamide compound. A solvent employed in this reaction may be pyridine, N-methylmorpholine and the like. Additionally, in a solvent such as N,N-dimethylformamide, methylene chloride, chloroform and the like, the reaction may be performed by further employing trimethylamine, in an equivalent ratio of 1.2 to methyl 4-aminobenzoate or 4-aminophenylacetic acid methylester. Most preferably, it may be pyridine. Further, the reaction may be preferably performed at a

temperature of 10~20℃. At a lower temperature than this, methyl 4-aminobenzoate or 4-aminophenylacetic acid methylester may remain unreacted and it is difficult to withdraw it from the product. While, at a higher temperature than 20℃, the anhydride may be hydrolyzed, resulting in the decrease of the yield of the product.

Benzamide compound formed herein may be reacted with an alkyl halide in a solvent of N,N-dimethylformamide, to produce a benzamide compound with an alkyl group substituted for amide bond thereof. Herein, as a base, sodium hydride may be employed in an equivalent ratio of 1.2 to benzamide. Also, alkyl halide may be employed in an equivalent ratio of 1.2 to benzamide. As an alkyl halide, it may include bromomethane, bromoethane, bromopropane, bromo-isopropane, bromobutane, bromo-*tert*-butane and the like.

Subsequently, methylester of benzamide with or without alkyl group substituted to amide bond may be hydrolyzed to an acid. Then, the acid formed may be converted to an anhydride by employing ethyl chloroformate. Herein, ethyl chloroformate may be employed in an equivalent ratio of 1.2 to the acid. A solvent employed herein may be pyridine, N-methylmorpholine and the like.

Then, the anhydride formed in said step may be reacted with hydroxylamine hydrochloride or N-methyl hydroxylamine hydrochloride, to produce a hydroxamic acid compound. A solvent employed in this reaction may be pyridine, N-methylmorpholine and the like. Additionally, in a solvent such as N,N-dimethylformamide, methylene chloride, chloroform and the like, the reaction may be performed by further employing triethylamine, in an equivalent ratio of 1.2 to hydroxylamine hydrochloride. Most preferably, it may be pyridine. Further, the reaction may be preferably performed at a temperature of 0~10℃. At a lower temperature than this, hydroxylamine hydrochloride or N-methyl hydroxylamine hydrochloride may remain unreacted, resulting in the decrease of the yield of the product. While, at a higher temperature than this, by-products

reacting with hydroxyl group of hydroxylamine or N-methyl hydroxylamine may be produced and it is difficult to withdraw it from the product.

The other method 2 for preparing the present hydroxamic acid derivative may comprise the steps of:

(a) Reacting aniline or adamantamine with monomethylterephthalate, to produce a benzamide compound;

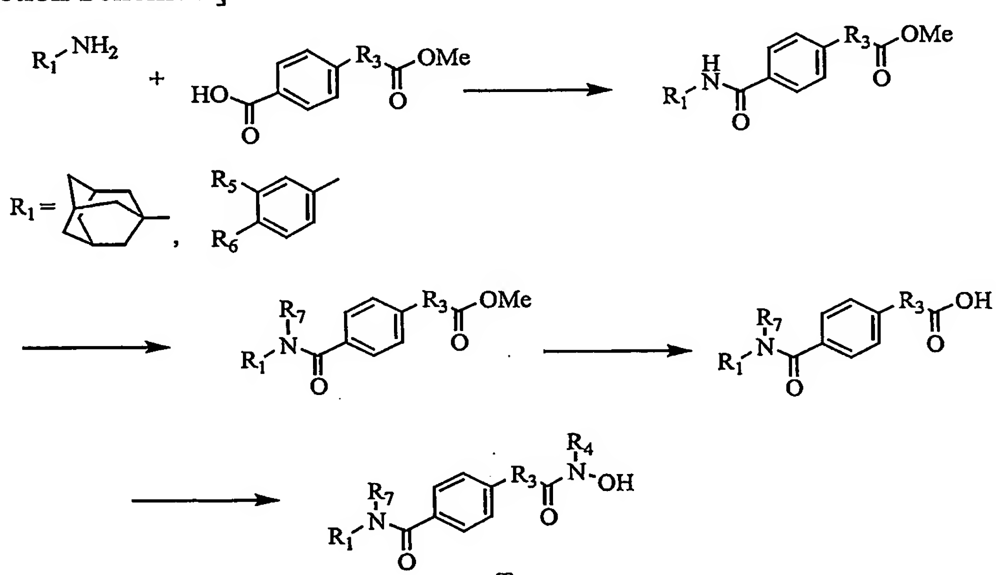
(b) Substituting an alkyl group for amide bond of benzamide formed in said step;

(c) Hydrolyzing methylester of benzamide or alkyl-substituted benzamide compounds formed in said steps, to produce an acid; and

(d) Reacting said acid with hydroxylamine hydrochloride or N-methyl hydroxylamine hydrochloride, to produce a hydroxamic acid derivative

and may be exemplified by the following reaction scheme 2:

[Reaction Scheme 2]



(I)

wherein, R_5 and R_6 each independently represents a hydrogen atom, a C_1-C_{10} alkyl group or a C_3-C_6 cyclic alkyl group; R_2 is CONH, NHCO, $CONR_7$ or NR_7CO, herein, R_7 represents a C_1-C_{10} alkyl group; R_3 is $-(CH)_n-$, herein, n = 0 or

1; and R_4 is a hydrogen atom or a C_1-C_{10} alkyl group.

As shown in the reaction scheme 2, firstly, monomethylterephthalate may be converted to an anhydride by employing ethyl chloroformate. Then, the anhydride may be reacted with aniline or adamantamine, to produce a benzamide compound. The next reactions may be performed by the same procedure described in the reaction scheme 1.

Hydroxamic acid derivatives of the formula (I) obtained in said methods may include, but not limited hereto,

1. N-[4-(N-hydroxycarbamoyl)phenyl] benzamide,
2. N-[4-(N-hydroxycarbamoyl)phenyl][4-methylphenyl] carboxyamide,
3. N-[4-(N-hydroxycarbamoyl)phenyl][3-methylphenyl] carboxyamide,
4. N-[4-(N-hydroxycarbamoyl)phenyl][4-ethylphenyl] carboxyamide,
5. N-[4-(N-hydroxycarbamoyl)phenyl][4-propylphenyl] carboxyamide,
6. N-[4-(N-hydroxycarbamoyl)phenyl][4-isopropylphenyl] carboxyamide,
7. N-[4-(N-hydroxycarbamoyl)phenyl][4-butylphenyl] carboxyamide,
8. N-[4-(N-hydroxycarbamoyl)phenyl][4-*tert*-butylphenyl] carboxyamide,
9. N-[4-(N-hydroxycarbamoyl)phenyl][3,4-dimethylphenyl] carboxyamide,
10. N-[4-(N-hydroxycarbamoyl)phenyl] adamantyl carboxyamide,
11. adamantyl-N-[4-(N-hydroxy-N-methylcarbamoyl)phenyl] carboxyamide,
12. N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-benzamide,
13. N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[4-methylphenyl] carboxyamide,
14. N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[3-methylphenyl] carboxyamide,
15. N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[4-ethylphenyl]

carboxyamide,

16. N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[4-propylphenyl] carboxyamide,

17. N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[4-isopropylphenyl] carboxyamide,

18. N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[4-butylphenyl] carboxyamide,

19. N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[4-*tert*-butylphenyl] carboxyamide,

20. N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[3,4-dimethylphenyl] carboxyamide,

21. N-[4-(N-hydroxycarbamoyl)phenyl] adamantyl-N-methylcarboxyamide,

22. adamantyl-N-[4-(N-hydroxy-N-methylcarbamoyl)phenyl]-N-methylcarboxyamide,

23. N-[4-(N-hydroxycarbamoylmethyl)phenyl] benzamide,

24. N-[4-(N-hydroxycarbamoylmethyl)phenyl][4-methylphenyl] carboxyamide,

25. N-[4-(N-hydroxycarbamoylmethyl)phenyl][3-methylphenyl] carboxyamide,

26. N-[4-(N-hydroxycarbamoylmethyl)phenyl][4-ethylphenyl] carboxyamide,

27. N-[4-(N-hydroxycarbamoylmethyl)phenyl][4-propylphenyl] carboxyamide,

28. N-[4-(N-hydroxycarbamoylmethyl)phenyl][4-isopropylphenyl] carboxyamide,

29. N-[4-(N-hydroxycarbamoylmethyl)phenyl][4-butylphenyl] carboxyamide,

30. N-[4-(N-hydroxycarbamoylmethyl)phenyl][4-*tert*-butylphenyl] carboxyamide,

31. N-[4-(N-hydroxycarbamoylmethyl)phenyl][3,4-dimethylphenyl] carboxyamide,

32. N-[4-(N-hydroxycarbamoylmethyl)phenyl] adamantyl carboxyamide,

33. 2-[4-(adamantylcarbonylamino)phenyl]-N-hydroxy-N-methylacetamide,
34. [4-(N-hydroxycarbamoyl)phenyl]-N-benzamide,
35. [4-(N-hydroxycarbamoyl)phenyl]-N-[4-methylphenyl] carboxyamide,
36. [4-(N-hydroxycarbamoyl)phenyl]-N-[3-methylphenyl] carboxyamide,
37. [4-(N-hydroxycarbamoyl)phenyl]-N-[4-ethylphenyl] carboxyamide,
38. [4-(N-hydroxycarbamoyl)phenyl]-N-[4-propylphenyl] carboxyamide,
39. [4-(N-hydroxycarbamoyl)phenyl]-N-[4-isopropylphenyl] carboxyamide,
40. [4-(N-hydroxycarbamoyl)phenyl]-N-[4-butylphenyl] carboxyamide,
41. [4-(N-hydroxycarbamoyl)phenyl]-N-[4-*tert*-butylphenyl] carboxyamide,
42. [4-(N-hydroxycarbamoyl)phenyl]-N-[3,4-dimethylphenyl] carboxyamide,
43. [4-(N-hydroxycarbamoyl)phenyl]-N-adamantyl carboxyamide,
44. N-adamantyl [4-(N-hydroxy-N-methylcarbamoyl)phenyl] carboxyamide,
45. [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-benzamide,
46. [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[4-methylphenyl] carboxyamide,
47. [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[3-methylphenyl] carboxyamide,
48. [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[4-ethylphenyl] carboxyamide,
49. [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[4-propylphenyl] carboxyamide,
50. [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[4-isopropylphenyl] carboxyamide,
51. [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[4-butylphenyl] carboxyamide,
52. [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[4-*tert*-butylphenyl] carboxyamide,
53. [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[3,4-dimethylphenyl]

carboxyamide,

54. [4-(N-hydroxycarbamoyl)phenyl]-N-adamantyl-N-methylcarboxyamide, and

55. N-adamantyl [4-(N-hydroxy-N-methylcarbamoyl)phenyl]-N-methylcarboxyamide.

Hydroxamic acid derivatives of the formula (I) obtained in said methods is a retinoid and function as an agonist to retinoic acid receptor and, based on retinoid's efficacy, can promote collagen biosynthesis and inhibit the expressions of collagenase, i.e. an enzyme for decomposing collagen and of elastase, i.e. an enzyme for decomposing elastin. Therefore, hydroxamic acid derivatives of the formula (I) provided by the present invention may be incorporated into medicines or external applications for improving skin elasticity.

PREFERRED EMBODIMENT OF THE INVENTION

The methods for preparing hydroxamic acid derivatives according to the present invention will be described in more detail by way of the following examples. However, these examples are provided for the purpose of illustration only and should not be construed as limiting the scope of the invention, which will be apparent to one skilled in the art.

<Example 1> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl] benzamide

20.0g (0.16mol) of benzoic acid was dissolved in 250mℓ of pyridine and then was cooled in a ice bath of 10℃. Thereto, 23.1g (0.21mol) of ethyl chloroformate was added dropwise for 30 minutes. The mixture was stirred at room temperature for 2 hours and then filtered to remove salts, to give an anhydride (30.2g, 0.15mol). 24.1G (0.16mol) of metyl aminobenzoate was

dissolved in 250mℓ of pyridine and then was cooled in a ice bath of 10℃. Thereto, the anhydride formed in the previous step was added dropwise for 30 minutes. The mixture was stirred for another 2 hours. After distillation of the solvent, the residue was dissolved in 300mℓ of ethyl acetate. The ethyl acetate solution was washed with 5% hydrochloric acid and with distilled water, dried over magnesium sulfate, decolorized with active charcoal, and then filtered. The filtrate was dried under reduced pressure, to give methyl 4-(phenylcarbonylamino) benzoate (34.7g, 85% yield) as a pale yellow solid.

Subsequently, 34.7g of methyl 4-(phenylcarbonylamino) benzoate was dissolved in 500mℓ of methanol and thereto 50mℓ of 10% KOH was added. After stirring for 3 hours, the mixture was neutralized with hydrochloric acid and then filtered, to give an acid compound, 4-(phenylcarbonylamino) benzoic acid (26.2g, 80% yield).

4-(phenylcarbonylamino) benzoic acid formed (24.1g, 0.10mol) was dissolved in 200mℓ of pyridine and then was cooled in a ice bath of 10℃. Thereto, 22.9g (0.13mol) of ethyl chloroformate was added dropwise for 30 minutes. The mixture was stirred at room temperature for 2 hours and then filtered to remove salts, to give an anhydride (38.7g, 0.12mol).

6.9g (0.10mol) of hydroxylamine hydrochloride was dissolved in 100mℓ of pyridine and then was cooled in a ice bath of 10℃. Thereto, the anhydride formed in the previous step was added dropwise for 30 minutes. The mixture was stirred for another 2 hours. After distillation of the solvent, the residue was dissolved in 300mℓ of ethyl acetate. The ethyl acetate solution was washed with 5% hydrochloric acid and with distilled water, dried over magnesium sulfate, decolorized with active charcoal, and then filtered. The filtrate was dried under reduced pressure, to give a final product, N-[4-(N-hydroxycarbamoyl)phenyl] benzamide (16.6g, 65% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.53$

^{1}H-NMR(DMSO-d_6): δ11.23(s, 1H), 10.39(s, 1H), 9.04(s, 1H), 8.01(m, 5H), 7.64(m, 4H).

<u><Example 2> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl][4-methylphenyl] carboxyamide</u>

Except that 4-methylbenzoic acid was used instead of benzoic acid, the same procedure described in Example 1 was performed to give the title compound (11.9g, 44% yield) as a pale yellow solid.

TLC (in ethyl acetate: hexane = 1:1); $R_f = 0.51$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.41(s, 1H), 9.07(s, 1H), 7.94(m, 4H), 7.80(d, 2H, J = 7.8Hz), 7.49(d, 2H, J = 7.8Hz), 2.33(s, 3H).

<u><Example 3> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl][3-methylphenyl] carboxyamide</u>

Except that 3-methylbenzoic acid was used instead of benzoic acid, the same procedure described in Example 1 was performed to give the title compound (11.2g, 43% yield) as a pale yellow solid.

TLC (in ethyl acetate: hexane = 1:1); $R_f = 0.50$

^{1}H-NMR(DMSO-d_6): δ11.21(s, 1H), 10.39(s, 1H), 9.05(s, 1H), 7.90(m, 6H), 7.23(m, 2H), 2.40(s, 3H).

<u><Example 4> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl][4-ethylphenyl] carboxyamide</u>

Except that 4-ethylbenzoic acid was used instead of benzoic acid, the same procedure described in Example 1 was performed to give the title compound (11.4g, 39% yield) as a pale yellow solid.

TLC (in ethyl acetate: hexane = 1:4); $R_f = 0.54$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.43(s, 1H), 9.05(s, 1H), 7.91(m, 4H),

7.81(d, 2H, J = 7.8Hz), 7.50(d, 2H, J = 7.8Hz), 2.51(m, 2H), 1.19(m, 3H).

<Example 5> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl][4-propylphenyl] carboxyamide

Except that 4-propylbenzoic acid was used instead of benzoic acid, the same procedure described in Example 1 was performed to give the title compound (12.5g, 42% yield) as a pale yellow solid.

TLC (in ethyl acetate: hexane = 1:1); $R_f = 0.55$

^{1}H-NMR(DMSO-d_6): δ11.23(s, 1H), 10.40(s, 1H), 9.03(s, 1H), 7.92(m, 4H), 7.83(d, 1H, J = 7.8Hz), 7.48(d, 1H, J = 7.8Hz), 2.60(m, 2H), 1.51(m, 2H), 0.95(m, 3H).

<Example 6> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl][4-isopropylphenyl] carboxyamide

Except that 4-isopropylbenzoic acid was used instead of benzoic acid, the same procedure described in Example 1 was performed to give the title compound (14.3g, 48% yield) as a pale yellow solid.

TLC(in ethyl acetate : hexane = 1:1); $R_f = 0.50$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.41(s, 1H), 9.07(s, 1H), 7.94(m, 4H), 7.80(d, 2H, J = 7.8Hz), 7.49(d, 2H, J = 7.8Hz), 2.80(m, 1H), 1.30(d, 6H, J = 6.9Hz).

<Example 7> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl][4-butylphenyl] carboxyamide

Except that 4-butylbenzoic acid was used instead of benzoic acid, the same procedure described in Example 1 was performed to give the title compound (12.8g, 41% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.53$

^{1}H-NMR(DMSO-d_6): 11.20(s, 1H), 10.42(s, 1H), 9.06(s, 1H), 7.94(m, 4H), 7.80(d, 2H, J = 7.8Hz), 7.49(d, 2H, J = 7.8Hz), 2.60(m, 2H), 1.60(m, 2H), 1.41(m, 2H), 0.95(m, 3H).

<Example 8> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl][4-*tert*-butylphenyl] carboxyamide

Except that 4-*tert*-butylbenzoic acid was used instead of benzoic acid, the same procedure described in Example 1 was performed to give the title compound (11.8g, 46% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.51

^{1}H-NMR(DMSO-d_6): 11.20(s, 1H), 10.41(s, 1H), 9.07(s, 1H), 7.92(m, 4H), 7.81(d, 2H, J = 7.8Hz), 7.51(d, 2H, J = 7.8Hz), 1.25(s, 9H).

<Example 9> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl][3,4-dimethylphenyl] carboxyamide

Except that 3,4-dimethylbenzoic acid was used instead of benzoic acid, the same procedure described in Example 1 was performed to give the title compound (11.9g, 44% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.53

^{1}H-NMR(DMSO-d_6): δ11.23(s, 1H), 10.40(s, 1H), 9.05(s, 1H), 7.93(m, 3H), 7.80(d, 2H, J = 7.8Hz), 7.50(d, 2H, J = 7.8Hz), 2.47(s, 3H), 2.45(s, 3H).

<Example 10> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl] adamantyl carboxyamide

Except that adamatanecarboxylic acid was used instead of benzoic acid, the same procedure described in Example 1 was performed to give the title compound (16.6g, 65% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.53

^{1}H-NMR(DMSO-d_6): δ11.22(s, 1H), 9.24(s, 1H), 8.87(s, 1H), 7.76(m, 4H), 1.96(m, 3H), 1.85(m, 6H), 1.64(m, 6H).

<Example 11> Preparation of adamantyl-N-[4-(N-hydroxy-N-methylcarbamoyl)phenyl] carboxyamide

Except that N-methyl hydroxylamine hydrochloride was used instead of hydroxylamine hydrochloride, the same procedure described in Example 10 was performed to give the title compound (11.2g, 43% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.50

^{1}H-NMR(DMSO-d_6): δ9.98(s, 1H), 9.12(s, 1H), 7.55(m, 4H), 3.09(s, 3H), 1.94(m, 3H), 1.87(m, 6H), 1.62(m, 6H).

<Example 12> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-benzamide

Methyl 4-(phenylcarbonylamino) benzoate (34.7g, 0.16mol) obtained in the intermediate step of Example 1 was dissolved in 250mℓ of N,N-dimethylformamide and then was cooled in a ice bath of 10℃. Thereto sodium hydride (20.7g, 0.16mol) in 50mℓ of N,N-dimethylformamide was added dropwise. Subsequently, bromomethane (32g, 0.16mol) was added dropwise to this mixture and further stirred for 1 hour. After stirring for another 2 hours, the mixture was distilled to remove the solvent and then the residue was dissolved in 300mℓ of ethyl acetate. The ethyl acetate solution was washed with 5% hydrochloric acid and with distilled water, dried over magnesium sulfate, decolorized with active charcoal, and then filtered. The filtrate was dried under reduced pressure, to give methyl 4-(phenylcarbonylamino)-N-methyl-benzoate (33.5g, 85% yield) as a pale yellow solid.

The subsequent procedures were the same as described in Example 1, to

give the title compound (12.8g, 38% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.52$

^{1}H-NMR(DMSO-d_6): δ11.23(s, 1H), 10.39(s, 1H), 9.04(s, 1H), 8.01(m, 5H), 7.64(m, 4H), 3.32(s, 3H).

<Example 13> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[4-methylphenyl] carboxyamide

Except that methyl 4-[(4-methylphenyl)carbonylamino] benzoate obtained in the intermediate step of Example 2 was used, the procedure described in Example 12 was performed to give the title compound (12.2g, 44% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.53$

^{1}H-NMR(DMSO-d_6): δ11.21(s, 1H), 10.41(s, 1H), 9.08(s, 1H), 7.94(m, 4H), 7.83(d, 2H, J = 7.8Hz), 7.52(d, 2H, J = 7.8Hz), 3.30(s, 3H), 2.45(s, 3H).

<Example 14> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[3-methylphenyl] carboxyamide

Except that methyl 4-[(3-methylphenyl)carbonylamino] benzoate obtained in the intermediate step of Example 3 was used, the procedure described in Example 12 was performed to give the title compound (12.2g, 44% yield) as a pale yellow solid.

TLC(in ethyl acetate : hexane = 1:1); $R_f = 0.51$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.43(s, 1H), 9.07(s, 1H), 7.93(m, 6H), 7.20(m,2H), 3.32(s, 3H), 2.44(s, 3H).

<Example 15> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[4-ethylphenyl] carboxyamide

Except that methyl 4-[(4-ethylphenyl)carbonylamino] benzoate obtained in

the intermediate step of Example 4 was used, the procedure described in Example 12 was performed to give the title compound (10.4g, 42% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:4); $R_f = 0.50$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.43(s, 1H), 9.05(s, 1H), 7.91(m, 4H), 7.81(d, 2H, J = 7.8Hz), 7.50(d, 2H, J = 7.8Hz), 3.31(s, 3H), 2.51(m, 2H), 1.40(m, 3H).

<Example 16> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[4-propylphenyl] carboxyamide

Except that methyl 4-[(4-propylphenyl)carbonylamino] benzoate obtained in the intermediate step of Example 5 was used, the procedure described in Example 12 was performed to give the title compound (11.4g, 43% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.55$

^{1}H-NMR(DMSO-d_6): δ11.23(s, 1H), 10.40(s, 1H), 9.03(s, 1H), 7.92(m, 4H), 7.83(d, 1H, J = 7.8Hz), 7.48(d, 1H, J = 7.8Hz), 3.34(s, 3H), 2.50(m, 2H), 1.51(m, 2H), 0.95(m, 3H).

<Example 17> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[4-isopropylphenyl] carboxyamide

Except that methyl 4-[(4-isopropylphenyl)carbonylamino] benzoate obtained in the intermediate step of Example 6 was used, the procedure described in Example 12 was performed to give the title compound (10.1g, 40% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.50$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.41(s, 1H), 9.07(s, 1H), 7.94(m, 4H),

7.80(d, 2H, J = 7.8Hz), 7.49(d, 2H, J = 7.8Hz), 3.35(s, 3H), 3.0(m, 1H), 1.30(d, 6H, J = 6.9Hz).

<Example 18> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[4-butylphenyl] carboxyamide

Except that methyl 4-[(4-butylphenyl)carbonylamino] benzoate obtained in the intermediate step of Example 7 was used, the procedure described in Example 12 was performed to give the title compound (12.1g, 47% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.53$

^{1}H-NMR(DMSO-d_6): 11.23(s, 1H), 10.41(s, 1H), 9.03(s, 1H), 7.92(m, 4H), 7.83(d, 2H, J = 7.8Hz), 7.53(d, 2H, J = 7.8Hz), 3.30(m, 3H), 2.49(m, 2H), 1.60(m, 2H), 1.41(m, 2H), 0.95(m, 3H).

<Example 19> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[4-*tert*-butylphenyl] carboxyamide

Except that methyl 4-[(4-*tert*-butylphenyl)carbonylamino] benzoate obtained in the intermediate step of Example 8 was used, the procedure described in Example 12 was performed to give the title compound (11.1g, 43% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.51$

^{1}H-NMR(DMSO-d_6): 11.21(s, 1H), 10.41(s, 1H), 9.05(s, 1H), 7.90(m, 4H), 7.79(d, 2H, J = 7.8Hz), 7.43(d, 2H, J = 7.8Hz), 3.32(s, 3H), 1.25(s, 9H).

<Example 20> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl]-N-methyl-[3,4-dimethylphenyl] carboxyamide

Except that methyl 4-[(3,4-dimethylphenyl)carbonylamino] benzoate obtained in the intermediate step of Example 9 was used, the procedure described in Example 12 was performed to give the title compound (12.2g, 44% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.52$

^{1}H-NMR(DMSO-d_6): δ11.25(s, 1H), 10.43(s, 1H), 9.07(s, 1H), 7.94(m, 3H), 7.82(d, 2H, J = 7.8Hz), 7.49(d, 2H, J = 7.8Hz), 3.30(s, 3H), 2.48(s, 3H), 2.45(s, 3H).

<u><Example 21> Preparation of N-[4-(N-hydroxycarbamoyl)phenyl] adamantyl-N-methylcarboxyamide</u>

Except that methyl 4-(adamantylcarbonylamino) benzoate obtained in the intermediate step of Example 10 was used, the procedure described in Example 12 was performed to give the title compound (12.8g, 38% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.53$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 9.23(s, 1H), 7.76(m, 4H), 3.74 (s, 3H), 1.96(m, 3H), 1.85(m, 6H), 1.64(m, 6H).

<u><Example 22> Preparation of adamantyl-N-[4-(N-hydroxy-N-methylcarbamoyl)phenyl]-N-methylcarboxyamide</u>

Except that N-methyl hydroxylamine hydrochloride was used instead of hydroxylamine hydrochloride, the procedure described in Example 21 was performed to give the title compound (11.4g, 39% yield) as a pale yellow solid.

TLC(in ethyl acetate : hexane = 1:4); $R_f = 0.54$

^{1}H-NMR(DMSO-d_6): δ9.95(s, 1H), 7.57(m, 4H), 3.72(s, 3H), 3.07(s, 3H), 1.94(m, 3H), 1.87(m, 6H), 1.62(m, 6H).

<Example 23> Preparation of N-[4-(N-hydroxycarbamoylmethyl)phenyl] benzamide

Except that 4-aminophenylacetic acid methylester was used instead of methyl 4-aminobenzoate, the procedure described in Example 1 was performed to give the title compound (10.0g, 39% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.53$

^{1}H-NMR(DMSO-d_6): δ11.23(s, 1H), 10.39(s, 1H), 9.04(s, 1H), 8.01(m, 5H), 7.64(m, 4H), 3.20(s, 2H).

<Example 24> Preparation of N-[4-(N-hydroxycarbamoylmethyl)phenyl][4-methylphenyl] carboxyamide

Except that 4-aminophenylacetic acid methylester was used instead of methyl 4-aminobenzoate, the procedure described in Example 2 was performed to give the title compound (11.9g, 44% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.52$

^{1}H-NMR(DMSO-d_6): δ11.22(s, 1H), 10.41(s, 1H), 9.07(s, 1H), 7.94(m, 4H), 7.80(d, 2H, J = 7.8Hz), 7.49(d, 2H, J = 7.8Hz), 3.21(s, 2H), 2.45(s, 3H).

<Example 25> Preparation of N-[4-(N-hydroxycarbamoylmethyl)phenyl][3-methylphenyl] carboxyamide

Except that 4-aminophenylacetic acid methylester was used instead of methyl 4-aminobenzoate, the same procedure described in Example 3 was performed to give the title compound (11.9g, 44% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.54$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.40(s, 1H), 9.04(s, 1H), 7.91(m, 6H), 7.22(m, 2H), 3.21(s, 2H), 2.44(s, 3H).

<Example 26> Preparation of N-[4-(N-hydroxycarbamoylmethyl)phenyl][4-ethylphenyl] carboxyamide

Except that 4-aminophenylacetic acid methylester was used instead of methyl 4-aminobenzoate, the procedure described in Example 4 was performed to give the title compound (12.9g, 45% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:4); R_f = 0.50

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.43(s, 1H), 9.05(s, 1H), 7.91(m, 4H), 7.81(d, 2H, J = 7.8Hz), 7.50(d, 2H, J = 7.8Hz), 3.21(s, 2H), 2.51(m, 2H), 1.40(m, 3H).

<Example 27> Preparation of N-[4-(N-hydroxycarbamoylmethyl)phenyl][4-propylphenyl] carboxyamide

Except that 4-aminophenylacetic acid methylester was used instead of methyl 4-aminobenzoate, the procedure described in Example 5 was performed to give the title compound (13.1g, 46% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.55

^{1}H-NMR(DMSO-d_6): δ11.23(s, 1H), 10.40(s, 1H), 9.03(s, 1H), 7.92(m, 4H), 7.83(d, 1H, J = 7.8Hz), 7.48(d, 1H, J = 7.8Hz), 3.20(s, 2H), 2.50(m, 2H), 1.51(m, 2H), 0.95(m, 3H).

<Example 28> Preparation of N-[4-(N-hydroxycarbamoylmethyl)phenyl][4-isopropylphenyl] carboxyamide

Except that 4-aminophenylacetic acid methylester was used instead of methyl 4-aminobenzoate, the procedure described in Example 6 was performed to give the title compound (11.1g, 43% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.50

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.41(s, 1H), 9.05(s, 1H), 7.93(m, 4H), 7.81(d, 2H, J = 7.8Hz), 7.48(d, 2H, J = 7.8Hz), 3.23(s, 2H), 3.01(m, 1H), 1.30(d,

6H, J = 6.9Hz).

<Example 29> Preparation of
N-[4-(N-hydroxycarbamoylmethyl)phenyl][4-butylphenyl] carboxyamide

Except that 4-aminophenylacetic acid methylester was used instead of methyl 4-aminobenzoate, the procedure described in Example 7 was performed to give the title compound (11.9g, 44% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.53

^{1}H-NMR(DMSO-d_6): 11.22(s, 1H), 10.40(s, 1H), 9.07(s, 1H), 7.91(m, 4H), 7.83(d, 2H, J = 7.8Hz), 7.52(d, 2H, J = 7.8Hz), 3.19(s, 2H), 2.49(m, 2H), 1.60(m, 2H), 1.41(m, 2H), 0.95(m, 3H).

<Example 30> Preparation of
N-[4-(N-hydroxycarbamoylmethyl)phenyl][4-*tert*-butylphenyl] carboxyamide

Except that 4-aminophenylacetic acid methylester was used instead of methyl 4-aminobenzoate, the procedure described in Example 8 was performed to give the title compound (12.0g, 42% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.51

^{1}H-NMR(DMSO-d_6): 11.22(s, 1H), 10.41(s, 1H), 9.06(s, 1H), 7.91(m, 4H), 7.83(d, 2H, J = 7.8Hz), 7.52(d, 2H, J = 7.8Hz), 3.20(s, 2H), 1.25(s, 9H).

<Example 31> Preparation of
N-[4-(N-hydroxycarbamoylmethyl)phenyl][3,4-dimethylphenyl] carboxyamide

Except that 4-aminophenylacetic acid methylester was used instead of methyl 4-aminobenzoate, the procedure described in Example 9 was performed to give the title compound (11.9g, 44% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.52

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.41(s, 1H), 9.05(s, 1H), 7.92(m, 3H),

7.80(d, 2H, J = 7.8Hz), 7.47(d, 2H, J = 7.8Hz), 3.21(s, 2H), 2.48(s, 3H), 2.44(s, 3H).

<Example 32> Preparation of N-[4-(N-hydroxycarbamoylmethyl)phenyl] adamantyl carboxyamide

Except that 4-aminophenylacetic acid methylester was used instead of methyl 4-aminobenzoate, the procedure described in Example 10 was performed to give the title compound (11.9g, 44% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.52$

^{1}H-NMR(DMSO-d_6): δ11.22(s, 1H), 9.25(s, 1H), 8.87(s, 1H), 7.76(m, 4H), 3.27(s, 2H), 1.96(m, 3H), 1.87(m, 6H), 1.63(m, 6H).

<Example 33> Preparation of 2-[4-(adamantlycarbonylamino)phenyl]-N-hydroxy-N-methylacetamide

Except that N-methyl hydroxylamine hydrochloride was used instead of hydroxylamine hydrochloride, the procedure described in Example 32 was performed to give the title compound (12.8g, 41% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.53$

^{1}H-NMR(DMSO-d_6): δ9.95(s, 1H), 9.12(s, 1H), 7.55(m, 4H), 3.27(s, 2H), 3.09(s, 3H), 1.94(m, 3H), 1.84(m, 6H), 1.60(m, 6H).

<Example 34> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-benzamide

Except that monomethylterephthalate and aniline were used instead of benzoic acid and methyl 4-aminobenzoate, the procedure described in Example 1 was performed to give the title compound (11.8g, 46% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.51$

^{1}H-NMR(DMSO-d_6):δ11.21(s, 1H), 10.29(s, 1H), 9.10(s, 1H), 8.01(m, 4H),

7.60(m, 5H).

<Example 35> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-[4-methylphenyl] carboxyamide

Except that onomethylterephthalate and 4-methylaniline were used instead of benzoic acid and methyl 4-aminobenzoate, the procedure described in Example 1 was performed to give the title compound (11.6g, 43% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.49$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.32(s, 1H), 9.11(s, 1H), 8.10(d, 2H, J = 7.8Hz), 7.98(d, 2H, J = 7.8Hz), 7.80(m, 4H), 2.44(s, 3H).

<Example 36> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-[3-methylphenyl] carboxyamide

Except that monomethylterephthalate and 3-methylaniline were used instead of benzoic acid and methyl 4-aminobenzoate, the procedure described in Example 1 was performed to give the title compound (11.6g, 43% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.49$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.32(s, 1H), 9.10(s, 1H), 8.10(m, 6H), 7.90(m, 2H), 2.42(s, 3H).

<Example 37> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-[4-ethylphenyl] carboxyamide

Except that monomethylterephthalate and 4-ethylaniline were used instead of benzoic acid and methyl 4-aminobenzoate, the procedure described in Example 1 was performed to give the title compound (12.8g, 45% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.51$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.33(s, 1H), 9.09(s, 1H), 8.12(d, 2H, J = 7.8Hz), 7.97(d, 2H, J = 7.8Hz), 7.81(m, 4H), 2.53(m, 2H), 1.42(m, 3H).

<Example 38> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-[4-propylphenyl] carboxyamide

Except that monomethylterephthalate and 4-propylaniline were used instead of benzoic acid and methyl 4-aminobenzoate, the procedure described in Example 1 was performed to give the title compound (11.6g, 39% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.53

^{1}H-NMR(DMSO-d_6): δ11.22(s, 1H), 10.33(s, 1H), 9.10(s, 1H), 8.13(d, 2H, J = 7.8Hz), 7.96(d, 2H, J = 7.8Hz), 7.88(m, 4H), 2.46(m, 2H), 1.50(m, 2H), 0.98(m, 3H).

<Example 39> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-[4-isopropylphenyl] carboxyamide

Except that monomethylterephthalate and 4-isopropylaniline were used instead of benzoic acid and methyl 4-aminobenzoate, the procedure described in Example 1 was performed to give the title compound (12.2g, 41% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.51

^{1}H-NMR (DMSO-d_6): δ11.20(s, 1H), 10.31(s, 1H), 9.11(s, 1H), 8.11(d, 2H, J = 7.8Hz), 7.99(d, 2H, J = 7.8Hz), 7.81(m, 4H), 2.99(m, 1H), 1.30(d, 6H, J = 6.9Hz).

<Example 40> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-[4-butylphenyl] carboxyamide

Except that monomethylterephthalate and 4-butylaniline were used instead

of benzoic acid and methyl 4-aminobenzoate, the procedure described in Example 1 was performed to give the title compound (12.8g, 41% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.51

^{1}H NMR (DMSO-d_6): δ11.21(s, 1H), 10.33(s, 1H), 9.13(s, 1H), 8.13(d, 2H, J = 7.8 Hz), 7.95(d, 2H, J = 7.8Hz), 7.88(m, 4H), 2.50(m, 2H), 2.00(m, 2H), 1.48(m, 2H), 0.95(m, 3H).

<Example 41> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-[4-*tert*-butylphenyl] carboxyamide

Except that monomethylterephthalate and 4-*tert*-butylaniline were used instead of benzoic acid and methyl 4-aminobenzoate, the procedure described in Example 1 was performed to give the title compound (12.8g, 41% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.51

^{1}H-NMR(DMSO-d_6): δ11.21(s, 1H), 10.31(s, 1H), 9.10(s, 1H), 8.15(d, 2H, J = 7.8 Hz), 7.94(d, 2H, J = 7.8Hz), 7.85(m, 4H), 1.40(s, 9H).

<Example 42> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-[3,4-dimethylphenyl] carboxyamide

Except that monomethylterephthalate and 3,4-dimethylaniline were used instead of benzoic acid and methyl 4-aminobenzoate, the procedure described in Example 1 was performed to give the title compound (11.6g, 43% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.49

^{1}H-NMR (DMSO-d_6): δ11.20(s, 1H), 10.30(s, 1H), 9.11(s, 1H), 8.10(d, 2H, J = 7.8Hz), 7.98(d, 2H, J = 7.8Hz), 7.84(m, 3H), 2.46(s, 3H), 2.42(s, 3H).

<Example 43> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-adamantyl carboxyamide

Except that monomethylterephthalate and adamantamine were used instead of adamantanecarboxylic acid and methyl 4-aminobenzoate, the procedure described in Example 10 was performed to give the title compound (11.8g, 46% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.51

^{1}H-NMR (DMSO-d_6): δ11.20(s, 1H), 9.21(s, 1H), 8.87(s, 1H), 7.73(m, 4H), 1.94(m, 3H), 1.84(m, 6H), 1.62(m, 6H).

<Example 44> Preparation of N-adamantyl [4-(N-hydroxy-N-methylcarbamoyl)phenyl] carboxyamide

Except that N-methyl hydroxylamine hydrochloride was used instead of hydroxylamine hydrochloride, the procedure described in Example 43 was performed to give the title compound (11.8g, 46% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.51

^{1}H-NMR(DMSO-d_6): δ9.99(s, 1H), 9.10(s, 1H), 7.53(m, 4H), 3.10(s, 3H), 1.91(m, 3H), 1.83(m, 6H), 1.60(m, 6H).

<Example 45> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-benzamide

Except that methyl 4-(phenylcarbamoyl) benzoate obtained in the intermediate step of Example 34 was used, the procedure described in Example 12 was performed to give the title compound (12.0g, 40% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.51

^{1}H-NMR(DMSO-d_6): δ11.21(s, 1H), 10.29(s, 1H), 9.10(s, 1H), 8.01(m, 4H), 7.60(m, 5H), 3.20(s, 3H).

<Example 46> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[4-methylphenyl] carboxyamide

Except that methyl 4-[(4-methylphenyl)carbamoyl] benzoate obtained in the intermediate step of Example 35 was used, the procedure described in Example 12 was performed to give the title compound (11.0g, 39% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.51$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.39(s, 1H), 9.11(s, 1H), 8.11(d, 2H, J = 7.8Hz), 7.98(d, 2H, J = 7.8Hz), 7.91(m, 4H), 3.20(s, 3H), 2.50(s, 3H).

<Example 47> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[3-methylphenyl] carboxyamide

Except that methyl 4-[(3-methylphenyl)carbamoyl] benzoate obtained in the intermediate step of Example 36 was used, the procedure described in Example 12 was performed to give the title compound (11.0g, 39% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.51$

^{1}H-NMR(DMSO-d_6): δ11.21(s, 1H), 10.30(s, 1H), 9.13(s, 1H), 8.10(m, 6H), 7.88(m, 2H), 2.50(s, 3H).

<Example 48> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[4-ethylphenyl] carboxyamide

Except that methyl 4-[(4-ethylphenyl)carbamoyl] benzoate obtained in the intermediate step of Example 37 was used, the procedure described in Example 12 was performed to give the title compound (12.0g, 40% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.55$

^{1}H-NMR(DMSO-d_6): δ11.22(s, 1H), 10.33(s, 1H), 9.10(s, 1H), 8.13(d, 2H, J

= 7.8Hz), 7.97(d, 2H, J = 7.8Hz), 7.89(m, 4H), 3.20(s, 3H), 2.46(m, 2H), 0.98(m, 3H).

<Example 49> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[4-propylphenyl] carboxyamide

Except that methyl 4-[(4-propylphenyl)carbamoyl] benzoate obtained in the intermediate step of Example 38 was used, the procedure described in Example 12 was performed to give the title compound (12.8g, 41% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.55

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.31(s, 1H), 9.13(s, 1H), 8.12(d, 2H, J = 7.8Hz), 7.96(d, 2H, J = 7.8Hz), 7.89(m, 4H), 3.20(s, 3H), 2.46(m, 2H), 1.50(m, 2H), 0.98(m, 3H).

<Example 50> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[4-isopropylphenyl] carboxyamide

Except that methyl 4-[(4-isopropylphenyl)carbamoyl] benzoate obtained in the intermediate step of Example 39 was used, the procedure described in Example 12 was performed to give the title compound (13.2g, 44% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.51

^{1}H-NMR(DMSO-d_6): δ11.21(s, 1H), 10.32(s, 1H), 9.15(s, 1H), 8.10(d, 2H, J = 7.8 Hz), 7.94(d, 2H, J = 7.8Hz), 7.83(m, 4H), 3.21(s, 3H), 2.50(m, 1H), 1.32(d, 6H, J = 6.9Hz).

<Example 51> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[4-butylphenyl] carboxyamide

Except that methyl 4-[(4-butylphenyl)carbamoyl] benzoate obtained in the intermediate step of Example 40 was used, the procedure described in Example 12 was performed to give the title compound (12.0g, 40% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.51$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.33(s, 1H), 9.14(s, 1H), 8.12(d, 2H, J = 7.8 Hz), 7.95(d, 2H, J = 7.8Hz), 7.84(m, 4H), 3.22(s, 3H), 2.50(m, 2H), 2.00(m, 2H), 1.48(m, 2H), 0.95(m, 3H).

<Example 52> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[4-*tert*-butylphenyl] carboxyamide

Except that methyl 4-[(4-*tert*-butylphenyl)carbamoyl] benzoate obtained in the intermediate step of Example 41 was used, the procedure described in Example 12 was performed to give the title compound (12.5g, 41% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.51$

^{1}H-NMR(DMSO-d_6): δ11.22(s, 1H), 10.33(s, 1H), 9.12(s, 1H), 8.11(d, 2H, J = 7.8 Hz), 7.96(d, 2H, J = 7.8Hz), 7.84(m, 4H), 3.20(s, 3H), 1.24(s, 9H).

<Example 53> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-methyl-N-[3,4-dimethylphenyl] carboxyamide

Except that methyl 4-[(3,4-dimethylphenyl)carbamoyl] benzoate obtained in the intermediate step of Example 42 was used, the procedure described in Example 12 was performed to give the title compound (11.0g, 39% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); $R_f = 0.51$

^{1}H-NMR(DMSO-d_6): δ11.20(s, 1H), 10.30(s, 1H), 9.11(s, 1H), 8.11(d, 2H, J = 7.8Hz), 7.95(d, 2H, J = 7.8Hz), 7.94(m, 3H), 3.20(s, 3H), 2.53(s, 3H), 2.50(s, 3H).

<Example 54> Preparation of [4-(N-hydroxycarbamoyl)phenyl]-N-adamantyl-N-methylcarboxyamide

Except that methyl 4-(N-adamantyl-N-methylcarbamoyl) benzoate obtained in the intermediate step of Example 43 was used, the procedure described in Example 12 was performed to give the title compound (11.8g, 46% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.51

^{1}H-NMR(DMSO-d_6): δ11.22(s, 1H), 9.22(s, 1H), 7.74(m, 4H), 3.71 (s, 3H), 1.93(m, 3H), 1.83(m, 6H), 1.63(m, 6H).

<Example 55> Preparation of N-adamantyl [4-(N-hydroxy-N-methylcarbamoyl)phenyl]-N-methyl carboxyamide

Except that N-methyl hydroxylamine hydrochloride was used instead of hydroxylamine hydrochloride, the procedure described in Example 54 was performed to give the title compound (11.8g, 46% yield) as a pale yellow solid.

TLC (in ethyl acetate : hexane = 1:1); R_f = 0.51

^{1}H-NMR(DMSO-d_6): δ9.93(s, 1H), 7.59(m, 4H), 3.70(s, 3H), 3.05(s, 3H), 1.92(m, 3H), 1.86(m, 6H), 1.60(m, 6H).

<Experimental Example 1> Affinity to retinoic acid receptor

This example illustrates affinities of hydroxamic acid derivatives obtained in Examples 1 to 55 to retinoic acid receptor, in comparison with retinol and retinoic acid.

Receptor-expression plasmid, pECE-RARα and pECE-RARγ were engineered by the prior method (*Mol. Cell. Biol.* 1996, 16, 1138-1149). RARE-tk-Luc, i.e. RARE reporter was obtained by inserting RARE fragment from b-RARE-tk-CAT into pGL3 luciferase basic vector. CV-1 cells were obtained from ATCC (American Type Culture Collection).

CV-1 cells were seeded into 96-well microtiter plate at 5,000 cells per well and cultured in DMEM (Dulbecco's Modified Eagle's Media) supplemented with 2.5% fetal bovine serum. 24 Hours later, the cells were transfected with 10ng of pECE-RARα, 10ng of pECE-RARγ, 100ng of reporter plasmid and 100ng of β-galactosidase-expression vector, using LipofectaminPlus (GIBCO BRL, grand island, NY). 24 Hours post-transfection, the cells were treated for 24 hours with hydroxamic acid derivatives of Examples 1~55 or retinol at a final concentration of 10^{-4}M or with retinoic acid at a final concentration of 10^{-5}M, which is 10 times lower concentration than those of the former.

[Table 1]

Materials	Luciferase activity RARα	Luciferase activity RARγ	Materials	Luciferase activity RARα	Luciferase activity RARγ
Control group (without	1000	5000	Example 27	13920	11300
Retinol	2500	6000	Example 28	12900	10700
Retinoic acid	25000	10000	Example 29	18900	10600
Example 1	10000	12000	Example 30	23500	12000
Example 2	12000	11200	Example 31	23100	10700
Example 3	11600	10000	Example 32	18000	10000
Example 4	12000	12300	Example 33	13400	11000
Example 5	18000	11000	Example 34	13900	11000
Example 6	14500	12300	Example 35	14500	11300
Example 7	12000	11700	Example 36	16700	11200
Example 8	10002	12000	Example 37	19000	10300

Example 9	12000	12000	Example 38	17500	10400
Example 10	11000	12000	Example 39	18700	10100
Example 11	11600	10000	Example 40	14300	11200
Example 12	14500	11300	Example 41	14300	11211
Example 13	12000	11200	Example 42	14500	11200
Example 14	18000	10300	Example 43	18900	10600
Example 15	14500	10400	Example 44	23100	10700
Example 16	12300	11200	Example 45	12300	11212
Example 17	12400	11700	Example 46	13200	11123
Example 18	12900	11400	Example 47	12200	11700
Example 19	10020	11200	Example 48	15500	11200
Example 20	12200	12300	Example 49	14500	12100
Example 21	12500	11200	Example 50	12300	11212
Example 22	12100	12400	Example 51	13400	12210
Example 23	13000	13200	Example 52	12400	12130
Example 24	12100	11210	Example 53	14500	12300
Example 25	13200	12100	Example 54	22500	11000
Example 26	17500	11200	Example 55	13400	11000

The above results for affinity to retinoic acid receptor indicate that hydroxamic acid derivatives obtained in Examples 1 to 55 can be regarded as retinoid compounds.

<Experimental Example 2> Effect on collagen biosynthesis

This example illustrates effects of hydroxamic acid derivatives obtained in Examples 1 to 55 on collagen biosynthesis, in comparison with retinol and retinoic acid.

Human fibroblasts were seeded into 24-well plate at 1×10^5 cells per well and then cultured to 90% of growth. Then, the fibroblastes were cultured in serum-free DMEM for 24 hours and treated with 10^{-4}M of hydroxamic acid

derivatives of Examples 1~55, retinol or retinoic acid in serum-free medium, and then incubated in CO_2 incubator for 24 hours.

For each supernatant, procollagen production was measured with procollagen type I ELISA kit. The results are shown in Table 2 and collagen biosynthesis was evaluated as a relative value, in consideration that the value of control group with no material treated is 100.

[Table 2]

Materials	Collagen biosynthesis (%)	Materials	Collagen biosynthesis (%)
Control group	100	Example 27	112
Retinol	120	Example 28	121
Retinoic acid	125	Example 29	132
Example 1	105	Example 30	121
Example 2	118	Example 31	109
Example 3	120	Example 32	125
Example 4	119	Example 33	112
Example 5	125	Example 34	108
Example 6	124	Example 35	111
Example 7	109	Example 36	121
Example 8	112	Example 37	121
Example 9	120	Example 38	109
Example 10	106	Example 39	105
Example 11	110	Example 40	108
Example 12	122	Example 41	115
Example 13	117	Example 42	116
Example 14	115	Example 43	130
Example 15	112	Example 44	107
Example 16	120	Example 45	108
Example 17	111	Example 46	121

Example 18	130	Example 47	112
Example 19	120	Example 48	107
Example 20	122	Example 49	109
Example 21	118	Example 50	110
Example 22	120	Example 51	121
Example 23	131	Example 52	127
Example 24	121	Example 53	122
Example 25	120	Example 54	121
Example 26	123	Example 55	108

<Experimental Example 3> Inhibition of collagenase expression

This example illustrates inhibition by hydroxamic acid derivatives obtained in Examples 1 to 55 of collagenase expression, in comparison with retinol and retinoic acid.

Human fibroblasts were seeded into 96-well microtiter plate at 5,000 cells per well and then cultured to 90% of growth in DMEM (Dulbecco's Modified Eagle's Media) supplemented with 2.5% fetal bovine serum. Then, the fibroblastes were cultured in serum-free DMEM for 24 hours and treated for 24 hours with 10^{-4}M of hydroxamic acid derivatives of Examples 1~55, retinol or retinoic acid in serum-free medium, and then the culture fluid was collected.

For each culture fluid, collagenase production was measured with collagenase kit (commercialized by AmershamPharmacia Biotech). Firstly, the culture fluid was added to 96-well plate spread with primary collagenase antibody and then antigen-antibody reaction was performed in an incubator for 3 hours. Later, chromophore-conjugated secondary antibody was added to the 96-well plate and then reacted for 15 minutes. Then, color former was added thereto, to induce development at room temperature for 15 minutes. 1M of sulfuric acid was added to stop the reaction. The reaction solution got yellow. The color density depends on the progress of the reaction. The absorbance of the

yellow 96-well plate was measured at 405㎚ using absorptiometer. Collagenase expression was calculated by the following equation 1. Herein, the absorbance of the culture fluid collected from the medium with no material treated was used as a control.

[Equation 1]

Collagenase expression (%) = (Absorbance of test group with said material treated /Absorbance of control group with no material treated)×100

The results for inhibition of collagenase expression in the cells are shown in Table 3 and confirmed that hydroxamic acid derivatives of the present invention could inhibit collagenase expression *in vitro*. Collagenase expression was evaluated as a relative value, in consideration that the value of control group with no material treated is 100.

[Table 3]

Materials	Collagenase expression (%)	Materials	Collagenase expression (%)
Control group	100	Example 27	87
Retinol	85	Example 28	67
Retinoic acid	60	Example 29	77
Example 1	78	Example 30	83
Example 2	68	Example 31	81
Example 3	80	Example 32	79
Example 4	78	Example 33	70
Example 5	79	Example 34	85
Example 6	85	Example 35	90
Example 7	84	Example 36	68
Example 8	90	Example 37	70

Example 9	65	Example 38	87
Example 10	75	Example 39	78
Example 11	81	Example 40	77
Example 12	64	Example 41	88
Example 13	70	Example 42	78
Example 14	72	Example 43	77
Example 15	79	Example 44	83
Example 16	80	Example 45	81
Example 17	81	Example 46	83
Example 18	78	Example 47	79
Example 19	70	Example 48	87
Example 20	68	Example 49	81
Example 21	69	Example 50	80
Example 22	77	Example 51	76
Example 23	77	Example 52	77
Example 24	76	Example 53	75
Example 25	70	Example 54	83
Example 26	78	Example 55	85

<Experimental Example 4> Inhibition of elastase expression

This example illustrates inhibition by hydroxamic acid derivatives obtained in Examples 1 to 55 of elastase expression, in comparison with retinol and retinoic acid.

Human fibroblasts were seeded into 96-well microtiter plate at 5,000 cells per well and then cultured to 90% of growth in DMEM (Dulbecco's Modified Eagle's Media) supplemented with 2.5% fetal bovine serum. Then, the fibroblastes were cultured in serum-free DMEM for 24 hours and treated for 24 hours with 10^{-4}M of hydroxamic acid derivatives of Examples 1~55, retinol or retinoic acid in serum-free medium, and then the culture fluid was collected.

For each culture fluid, elastase production was measured with elastase kit

(commercialized by AmershamPharmacia Biotech). Firstly, the culture fluid was added to 96-well plate spread with primary elastase antibody and then antigen-antibody reaction was performed in an incubator for 3 hours. Later, chromophore-conjugated secondary antibody was added to the 96-well plate and then reacted for 15 minutes. Then, color former was added thereto, to induce development at room temperature for 15 minutes. 1M of sulfuric acid was added to stop the reaction. The reaction solution got yellow. The color density depends on the progress of the reaction. The absorbance of the yellow 96-well plate was measured at 405nm using absorptiometer. Elastase expression was calculated by the following equation 2. Herein, the absorbance of the culture fluid collected from the medium with no material treated was used as a control.

[Equation 2]

Elastase expression (%) = (Absorbance of test group with said material treated /Absorbance of control group with no material treated)×100

The results for inhibition of elastase expression in the cells are shown in Table 4 and confirmed that hydroxamic acid derivatives of the present invention could inhibit elastase expression *in vitro*. Elastase expression was evaluated as a relative value, in consideration that the value of control group with no material treated is 100.

[Table 4]

Materials	Elastase expression (%)	Materials	Elastase expression (%)
Control group	100	Example 27	87
Retinol	88	Example 28	79
Retinoic acid	68	Example 29	70

Example 1	79	Example 30	69
Example 2	78	Example 31	63
Example 3	69	Example 32	74
Example 4	70	Example 33	82
Example 5	78	Example 34	70
Example 6	79	Example 35	71
Example 7	77	Example 36	79
Example 8	69	Example 37	80
Example 9	67	Example 38	69
Example 10	77	Example 39	87
Example 11	65	Example 40	90
Example 12	80	Example 41	78
Example 13	84	Example 42	76
Example 14	75	Example 43	70
Example 15	76	Example 44	63
Example 16	77	Example 45	81
Example 17	82	Example 46	80
Example 18	79	Example 47	83
Example 19	80	Example 48	87
Example 20	78	Example 49	87
Example 21	78	Example 50	78
Example 22	70	Example 51	77
Example 23	79	Example 52	87
Example 24	82	Example 53	80
Example 25	80	Example 54	67
Example 26	86	Example 55	70

<Experimental Example 5> Primary skin irritation test on animals

1) Method

Test was performed using fifty-six (56) of healthy male rabbits whose backs were depilated. The compounds of Examples 1~55 were dissolved in solvent

(1,3-butylene glycol: ethanol = 7:3) to give 1% solution of test samples. 0.5ml of the test sample solution was applied to the right site of 2.5cm×2.5cm region on each of the depilated back. Left site with no sample treated was compared as a control. 24 hours or 72 hours later, skin abnormality such as erythema, crust and edema was observed. Skin response was scored according to "standard guide for toxicity test of foods and drugs", as shown in Table 5.

Based on the score of skin response, skin irritation was evaluated according to Draize's P.I.I.(Primary Irritation Index) and compared with retinoic acid. The results are shown in Table 6.

[Table 5]

Skin responses		Score
1) Erythema and crust	No erythema	0
	A slight erythema (scarcely visible)	1
	Significant erythema	2
	Severe erythema	3
	Crimson extremely-severe erythema and crust	4
2) Edema	No edema	0
	A slight edema (scarcely visible)	1
	Significant edema (distinct from periphery)	2
	Severe edema (swelled up about 1mm)	3
	Extremely-severe edema (swelled up 1mm or more and expanded out of the exposed site)	4

[Table 6]

Materials	P. I. I.	Evaluation	Materials	P. I. I.	Evaluation
Retinoic acid	1.830	Light irritation	Example 28	0.765	No irritation
Example 1	0.375	No irritation	Example 29	0.234	No irritation
Example 2	0.345	No irritation	Example 30	0.456	No irritation

Example 3	0.375	No irritation	Example 31	0.567	No irritation
Example 4	0.350	No irritation	Example 32	0.375	No irritation
Example 5	0.375	No irritation	Example 33	0.765	No irritation
Example 6	0.315	No irritation	Example 34	0.678	No irritation
Example 7	0.312	No irritation	Example 35	0.245	No irritation
Example 8	0.330	No irritation	Example 36	0.456	No irritation
Example 9	0.470	No irritation	Example 37	0.456	No irritation
Example 10	0.375	No irritation	Example 38	0.567	No irritation
Example 11	0.375	No irritation	Example 39	0.145	No irritation
Example 12	0.410	No irritation	Example 40	0.546	No irritation
Example 13	0.500	No irritation	Example 41	0.367	No irritation
Example 14	0.231	No irritation	Example 42	0.987	No irritation
Example 15	0.789	No irritation	Example 43	0.456	No irritation
Example 16	0.567	No irritation	Example 44	0.678	No irritation
Example 17	0.123	No irritation	Example 45	0.900	No irritation
Example 18	0.321	No irritation	Example 46	0.345	No irritation
Example 19	0.223	No irritation	Example 47	0.367	No irritation
Example 20	0.421	No irritation	Example 48	0.468	No irritation
Example 21	0.345	No irritation	Example 49	0.342	No irritation
Example 22	0.350	No irritation	Example 50	0.234	No irritation
Example 23	0.321	No irritation	Example 51	0.331	No irritation
Example 24	0.321	No irritation	Example 52	0.412	No irritation
Example 25	0.423	No irritation	Example 53	0.321	No irritation
Example 26	0.321	No irritation	Example 54	0.567	No irritation
Example 27	0.568	No irritation	Example 55	0.245	No irritation

As shown in Table 6, hydroxamic acid derivatives obtained in Examples 1 to 55 were confirmed to be non-irritative to the skin.

These results illustrate that hydroxamic acid derivatives of the present invention have the same efficacy in improving skin elasticity as that of retinol or

retinoic acid, and additionally good safety and less skin irritation, to be incorporated into skin-care external compositions for improving skin elasticity.

<Experimental Example 6> Phototoxicity test

Test was performed for twenty-five (25) of white guinea pigs whose backs were depilated and fixed. On both sides of the back, six(6) sites of 2㎝×2㎝, three(3) per side were sectioned. Right sites were compared as controls with no irradiation (UV non-irradiation sites) and left sites were irradiated (UV irradiation sites). As a negative control, vehicle of 1,3-butylene glycol:ethanol=7:3 and as a positive control, 0.1% 8-MOP(methoxypsoralene) were prepared, and then hydroxamic acid derivatives of Examples 1~55 were dissolved in 1,3-butylene glycol:ethanol=7:3, to give 1%(w/v) of solutions, of which each 50㎕ was applied.

30 Minutes later, right sites were shielded with aluminum foil and UVA(320~380㎚) was irradiated at a distance of about 10㎝ therefrom using Waldmann to the final energy of 15 J/㎠. After 24, 48 and 72 hours elapsed, skin response of guinea pig was observed. Erythema and edema were scored from 0 to 4, as shown in said Table 5 and skin response was evaluated by the sum of scores. Evaluation was estimated for each elapsed time, i.e. 24, 48 and 72 hours and maximum scores were selected, to calculate irritation index by the following equation 3. Then, phototoxic index was calculated by the following equation 4. The results are shown in Table 7.

[Equation 3]

Irritation index = (ΣMaximum of erythema + ΣMaximum of edema) / Number of animals

[Equation 4]

Phototoxic index = (Irritation index of UV irradiation site) – (Irritation index of

UV non-irradiation site)

[Table 7]

Materials	Phototoxic index	Evaluation	Materials	Phototoxic index	Evaluation
Example 1	0	No phototoxicity	Example 29	0	No phototoxicity
Example 2	0	No phototoxicity	Example 30	0	No phototoxicity
Example 3	0	No phototoxicity	Example 31	0	No phototoxicity
Example 4	0	No phototoxicity	Example 32	0	No phototoxicity
Example 5	0	No phototoxicity	Example 33	0	No phototoxicity
Example 6	0	No phototoxicity	Example 34	0	No phototoxicity
Example 7	0	No phototoxicity	Example 35	0	No phototoxicity
Example 8	0	No phototoxicity	Example 36	0	No phototoxicity
Example 9	0	No phototoxicity	Example 37	0	No phototoxicity
Example 10	0	No phototoxicity	Example 38	0	No phototoxicity
Example 11	0	No phototoxicity	Example 39	0	No phototoxicity
Example 12	0	No phototoxicity	Example 40	0	No phototoxicity
Example 13	0	No phototoxicity	Example 41	0	No phototoxicity
Example 14	0	No phototoxicity	Example 42	0	No phototoxicity
Example 15	0	No phototoxicity	Example 43	0	No phototoxicity
Example 16	0	No phototoxicity	Example 44	0	No phototoxicity
Example 17	0	No phototoxicity	Example 45	0	No phototoxicity
Example 18	0	No phototoxicity	Example 46	0	No phototoxicity
Example 19	0	No phototoxicity	Example 47	0	No phototoxicity
Example 20	0	No phototoxicity	Example 48	0	No phototoxicity
Example 21	0	No phototoxicity	Example 49	0	No phototoxicity
Example 22	0	No phototoxicity	Example 50	0	No phototoxicity
Example 23	0	No phototoxicity	Example 51	0	No phototoxicity
Example 24	0	No phototoxicity	Example 52	0	No phototoxicity
Example 25	0	No phototoxicity	Example 53	0	No phototoxicity
Example 26	0	No phototoxicity	Example 54	0	No phototoxicity

Example 27	0	No phototoxicity	Example 55	0	No phototoxicity
Example 28	0	No phototoxicity			

As shown in Table 7, hydroxamic acid derivatives obtained in Examples 1 to 55 were confirmed to have 0 of phototoxic index, which was lower value than 0.5, criterion value to be estimated as no phototoxicity.

Hydroxamic acid derivatives according to the present invention may be incorporated into skin-care external compositions. The present composition may be formulated into, but not limited to, cosmetic compositions such as skin softners, astringents, nutrient toilet water, nutrient creams, massage creams, essences, eye creams, eye essences, cleansing creams, cleansing foams, cleansing water, packs, powders, body lotions, body creams, body oils, body essences, make-up bases, foundations, hairdyes, shampoos, hair-conditioners and body cleansers; and pharmaceutical compositions such as ointment, gels, creams, patches, and sprays. And, each formulation may further contain bases and additives suitable for the preparation thereof, if necessary, whose kind and amount can be easily selected in this art.

<Formulation 1> Nutrient toilet water (Milk lotion)

Nutrient toilet water containing said hydroxamic acid derivatives obtained in Examples 1 to 55 was prepared.

Ingredients	Amount (wt%)
1. Distilled water	To 100
2. Glycerin	8.0
3. Butylene glycol	4.0
4. Extracts with hyaluronic acid	5.0
5. β-glucan	7.0

6. Carbomer	0.1
7. Hydroxamic acid derivative	q.s.
8. Caprylic/Capric triglyeride	8.0
9. Squalane	5.0
10. Cetearyl glucoside	1.5
11. Sorbitan stearate	0.4
12. Cetearyl alcohol	1.0
13. Preservative	q.s.
14. Perfume	q.s.
15. Pigments	q.s.
16. Triethanolamine	0.1

<Formulation 2> Nutrient cream

Nutrient cream containing said hydroxamic acid derivatives obtained in Examples 1 to 55 was prepared.

Ingredients	Amount (wt%)
1. Distilled water	To 100
2. Glycerin	3.0
3. Butylene glycol	3.0
4. Liquid paraffin	7.0
5. β-glucan	7.0
6. Carbomer	0.1
7. Hydroxamic acid derivative	q.s.
8. Caprylic/Capric triglyeride	3.0
9. Squalane	5.0
10. Cetearyl glucoside	1.5
11. Sorbitan stearate	0.4
12. Polysorbate 60	1.2
13. Preservative	q.s.
14. Perfume	q.s.

15. Pigments	q.s.
16. Triethanolamine	0.1

<Formulation 3> Massage cream

Massage cream containing said hydroxamic acid derivatives obtained in Examples 1 to 55 was prepared.

Ingredients	Amount (wt%)
1. Distilled water	To 100
2. Glycerin	8.0
3. Butylene glycol	4.0
4. Liquid paraffin	45.0
5. β-glucan	7.0
6. Carbomer	0.1
7. Hydroxamic acid derivative	q.s.
8. Caprylic/Capric triglyeride	3.0
9. Beeswax	4.0
10. Cetearyl glucoside	1.5
11. Sorbitan sesquioleate	0.9
12. Vaseline	3.0
13. Preservative	q.s.
14. Perfume	q.s.
15. Pigments	q.s.
16. Paraffin	1.5

<Formulation 4> Ointment

Ointment containing said hydroxamic acid derivatives obtained in Examples 1 to 55 was prepared.

Ingredients	Amount (wt%)
1. Distilled water	To 100

2. Glycerin	8.0
3. Butylene glycol	4.0
4. Liquid paraffin	15.0
5. β-glucan	7.0
6. Carbomer	0.1
7. Hydroxamic acid derivative	q.s.
8. Caprylic/Capric triglyeride	3.0
9. Squalane	1.0
10. Cetearyl glucoside	1.5
11. Sorbitan stearate	0.4
12. Cetearyl alcohol	1.0
13. Preservative	q.s.
14. Perfume	q.s.
15. Pigments	q.s.
16. Beeswax	4.0

INDUSTRIAL APPLICATION OF THE INVENTION

As described in the above, hydroxamic acid derivatives according to the present invention can promote collagen biosynthesis and inhibit the expressions of collagenase and elastase by interacting to retinoic acid receptor. Furthermore, they do not cause skin irritation and skin toxicity, which have been drawbacks of retinoid compounds to be solved. Therefore, they can be incorporated into medicines or skin-care external compositions for improving skin elasticity and preventing skin aging.